Molecular simulation of surface-modified polymer vesicle designed for gene and drug delivery

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ABSTRACT: Targeted gene and drug delivery holds a great potential for the successful treatment of many diseases. Approaching the tumor via blood circulation should allow several advantages over the local intratumoral injection such as reaching multiple distant metastases. One of the considerable problems preventing the creation of such a gene delivery carrier is inefficient site-specific targeting. Modification of nanoparticles with polymer e.g. poly(ethylene glycol) offers a reduction of non-specific binding to cell surfaces and improves the circulation time of the gene/drug delivery vehicles in blood. This work employ a novel molecular simulation technique to study the conformation, thermodynamic and orientational properties of polymer brushes to gain more fundamental information for the role of surface modification by grafted chain. Polymer models with end beads tethered on surface with the grafting density ranged from 0.5 to 1.5 nm^{-2} were considered. As the grafting density increases, chains become more stretched in the direction perpendicular to the surface. The profile of the chain end and inner bead density are seen to exhibit universal law in agreement with the prediction of SCF theory. The mean chain conformational path, surface energy and the structure of the interfacial area are also presented and compared with the theoretical prediction. These simulation results give an insight to the molecular design of the interface modification that may enhance more efficiency of targeted gene and drug delivery.

INTRODUCTION: Considerable research efforts have recently gone into the study of the nanostructure and physical properties of polymers end-grafted onto a solid surface. These systems are known as polymer brushes for sufficiently high polymer densities. The properties of brush depend on the density and the type of polymer molecules. Interfaces between polymers and solids play a key role in many industrial applications as adhesives, colloidal stabilizers, and lubricants. Of great importance is the practice of improving the stability of nanoparticles with polymer e.g. poly(ethylene glycol) which offers a reduction of non-specific binding to cell surfaces and improves the circulation time of the gene/drug delivery vehicles in blood. Establishing quantitative relations between chemical constitution and macroscopic properties of such systems and predicting their structure and properties is highly desirable, because this can tremendously facilitate the rational design of vesicle systems suitable for real application in drug delivery or gene therapy.

Detailed information like the polymer chain trajectory, fluctuation etc. can conveniently be obtained in a computer simulation and compared with the SCF theory. Unfortunately, little simulation work has been performed for chains with chemically realistic architectures. In this work, a novel computer simulation technique capable of probing the structure of the interface between the solid substrate and grafted polymer melts at a prescribed grafting density is developed. This simulation allows us to obtain detailed information about the conformational, structural, and thermodynamic properties near the solid substrate, while avoiding many of the assumptions invoked in the mesoscopic, SCF models, in analytical brush theories and past simulations of bead-spring or ideal chains.

MODEL AND SIMULATION: We study monodisperse grafted polymers, each chain containing N ethylene units, with $20 < N < 40$. The solid substrate was located at $z = 0$ and impenetrable. Beads were not allowed to move from $z = 0$ to -1. The total number of available surface sites is 40x40 (surface area = 86.6 nm^2). We choose periodic boundary conditions in the x and y directions, while the two boundary in z direction (at $z = 1$ and $z = M$, where $M > N$) are treated as hard impenetrable walls. The grafting density (σ) is from 0.92 to 1.85 nm^{-2}. To model the PE chain, RIS formalism is used to model the short-range intramolecular interactions. Long-range intra- and intermolecular interaction among nonbonded units are incorporated into the simulations using the Lennard-Jones potential for ethylene units with ε/k_B = 185 K and σ = 0.44 nm. Single bead and pivot moves on the lattice are accepted according to the Metropolis MC algorithm. Analysis is obtained as an ensemble average of the subsequent 10^6 MCS after equilibration. A snapshot is taken every 10,000 MCS during this period for analysis of the static properties.

RESULTS AND DISCUSSIONS

A. *Local melt density*

For the grafting densities studied, $\rho(z)$ exhibits two zones of reduced density corresponding to two boundaries: the substrate/melt and the melt/vacuum interfaces. In contrast, the density practically remains constant in the bulk region independent of σ. The reduced $\rho(z)$ values near the solid are mainly entropic origin caused by the presence of the boundary that limits the number of available conformation assumed by each grafted chain. The sigmoidal shape and the width of the profile at the upper boundary is typical of a melt/vacuum interface. The identification of the two zones where the melt density attains reduced values relative to the bulk demonstrates its power in elucidating some of the silent features underlying the structural and thermodynamic properties of grafted polymeric systems. These results are in contrast to the usual practice in analytical or numerical theoretical models of grafted melts which, in their majority, invoke the assumption of a constant density everywhere in the interfacial region.

B. *Conformational properties*

Information about the conformational properties can be extracted by studying the average chain conformational path defined as the average height $<z(i)>$ of backbone atom i above the grafting surface. The reduced mean height $\zeta(s)$ defined through $\zeta(s) = <z(i)>/ <z(1)>$ as a function of scaled coordinate $s = i/N$. $\zeta(s)$ is an increasing function of atom ranking position s which means that, on the average, grafted chains develop upward without any back folding. According to analytical brush theories,[5-6] this graph should lead to a universal curve, independent of σ. All curves are seen to superimpose reasonably well with the SCF result, $\zeta(s) = \sin(s\pi/2)$, and fall approximately on a single curve implying $<z_i>$ is a function of i/N only.

C. *Distribution of monomers*

Interestingly, the end monomers can be anywhere in the brush. Thus there is a systematic deviation from the SCF theory which predicts no end bead at z = 0. The SCF also suggests a scaling plot of $\rho_i(z)h\sin(i\pi/2N)$ versus $z/\{h\sin(i\pi/2N)\}$. Within the statistical accuracy of the simulation results, the curves obtained coincide, suggesting the existence of a master curve. However, the functional form of the master curve predicted is somewhat different than that of the curve derived by analytical theories.

D. *Orientation*

The profiles of the first-rank order parameter (from carbon atom *i* to *i*+2) $\langle P_1(\cos\theta)\rangle = <\cos\theta>$ are calculated as a function of *N* and σ where θ is the angle formed between a chord vector and *z* axis. The positive order parameter was found even at the outer edges of the grafted layer which demonstrate that, on average, the grafted chains develop outwards exactly as was inferred by the continuous increase of the function $\langle z(i)\rangle$ for large *i*. From the SCF theory, the profiles of the function $\lambda_1 = \frac{\langle P_1(\cos\theta)\rangle}{\sigma}$ should exhibits a universal behavior, independent of *N* and σ as $\lambda_1 = \cos\left(\frac{i\pi}{2N}\right)$. The data show a rough collapse except for monomers near the wall. This is expected since SCF theory does not take into account for the short range order effects near the wall. The MC data indicate the brush is less stretched but the stretching is quite uniform over the entire brush.

CONCLUSION: A methodology is presented for the study of grafted polymer melts through the coarse-grained PE model using lattice MC simulations. PE melt systems consisting of grafted chains as long as C_{80} were studied in a broad range of grafting densities. For melts consisting of only grafted chains, our simulation data verified many universal laws suggested by the analytical brush theories. However, the exact functional dependencies of certain descriptors of the brush conformational and structural characteristics on chain length and grafting density seem to be different from those derived analytically.

Keywords—Monte Carlo simulation, self-consistent field theory, rotational isomeric state model, polymer brushes, grafted polymer, gene/drug delivery

Reference

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